

MEETING ABSTRACT

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A molecular switch between the outer and the inner vestibules of the voltage-gated Na⁺ channel

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Background

Voltage-gated ion channels are transmembrane proteins that undergo complex conformational changes during their gating transitions. Both functional and structural data from K⁺ channels suggest that extracellular and intracellular parts of the pore communicate with each other via a trajectory of interacting amino acids. No crystal structures are available for voltage-gated Na⁺ channels but functional data suggest a similar intramolecular communication involving the inner and outer vestibules. However, the mechanism of such communication is unknown. Here, we report that amino acid I1575 in the middle of transmembrane segment 6 of domain IV (DIV-S6) in the rNa_v1.4 channel may act as molecular switch allowing for interaction between outer and inner vestibule.

Methods and results

Cysteine scanning mutagenesis of the internal part of DIV-S6 revealed that only mutations at site 1575 rescued the channel from a unique kinetic state ("ultra-slow inactivation", I_{US}) produced by the mutation K1237E in the selectivity filter. The fact that mutations at site 1575 modulate I_{US} produced by K1237E strongly suggests an interaction between these sites. To elucidate how I_{US} is generated, we "forced" large organic cations through the channel, which resulted in a significant linear correlation between the increase in the amplitude of recovery from I_{US} and the diameter of the permeating cations. Additionally, we show that a permeation pathway for the permanently charged lidocaine analogue QX222, opened by mutations at site 1575, is closed by the addition of K1237E to these I1575 mutants.

Conclusions

These results support the notion that an increase in the size of the selectivity filter produced by the mutation K1237E gives rise to an interaction of E1237 with I1575 of the adjacent S6 segment thereby generating IUS.

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